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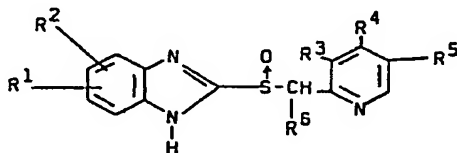
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54 Substituted pyridylsulfinylbenzimidazoles having gastric acid secretion properties, pharmaceutical preparations containing same, and intermediates for their preparation.

57 The present invention relates to novel compounds of the formula



wherein R<sup>1</sup> and R<sup>2</sup> are same or different and are each hydrogen, alkyl, halogen, carbomethoxy, carbethoxy, alkoxy, or alkanoyl, R<sup>3</sup> is hydrogen, methyl or ethyl, R<sup>4</sup> and R<sup>5</sup> are same or different and are each hydrogen, methyl, methoxy, ethoxy, methoxyethoxy or ethoxyethoxy whereby R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> are not all hydrogen, and whereby when two of R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> are hydrogen the third of R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> is not methyl. The compounds are potent gastric acid secretion inhibitors.

EP 0 005 129 A1

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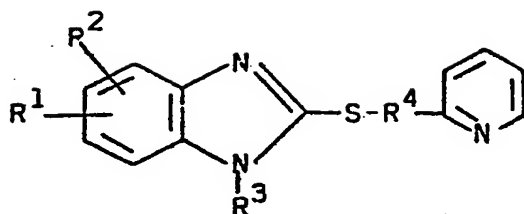
Substituted pyridylsulfinylbenzimidazoles having gastric acid secretion properties, pharmaceutical preparations containing same, and intermediates for their preparation

The present invention relates to new compounds having valuable properties in affecting gastric acid secretion in mammals, including man, as well as the process for their preparation, method of affecting gastric acid secretion  
5 and pharmaceutical preparations containing said novel compounds.

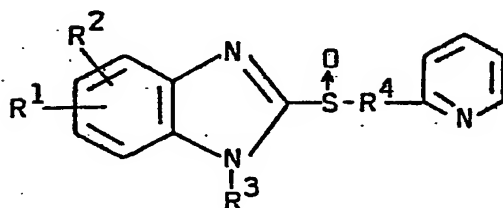
The object of the present invention is to obtain compounds which affect gastric acid secretion, and which inhibit  
10 exogenously or endogenously stimulated gastric acid secretion. These compounds can be used in the treatment of peptic ulcer disease.

It is previously known that compounds of the formulas I and II

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(I)

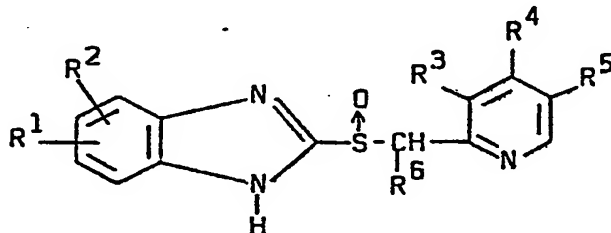


(II)

wherein  $R^1$  and  $R^2$  are each selected from the group consisting of hydrogen, alkyl, halogen, cyano, carboxy, carboxy-alkyl, carboalkoxy, carboalkoxyalkyl, carbamoyl, carbamoyloxy, hydroxy, alkoxy, hydroxyalkyl, trifluoromethyl and acyl in any position,  $R^3$  is selected from the group consisting of hydrogen, alkyl, acyl, carboalkoxy, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl, alkylcarbonylmethyl, alkoxy-carbonylmethyl, and alkylsulphonyl, and  $R^4$  is selected from the group consisting of straight and branched alkylene groups having 1 to 4 carbon atoms, whereby at most one methylene group is present between S and the pyridyl group, and whereby the pyridyl group may be further substituted with alkyl or halogen, possess inhibiting effect of gastric acid secretion.

It has now, however, surprisingly been found that the compounds defined below possess a still greater inhibiting effect than those given above.

Compounds of the invention are those of the general formula III



(III)

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wherein  $R^1$  and  $R^2$  are same or different and are each selected from the group consisting of hydrogen, alkyl, halogen, carbomethoxy, carbethoxy, alkoxy, and alkanoyl,  $R^6$  is selected from the group consisting of hydrogen, methyl, and ethyl, and  $R^3$ ,  $R^4$  and  $R^5$  are same or different and are each selected from the group consisting of hydrogen, methyl, methoxy, ethoxy, methoxyethoxy and ethoxyethoxy whereby  $R^3$ ,  $R^4$ , and  $R^5$  are not all hydrogen, and whereby when two of  $R^3$ ,  $R^4$ , and  $R^5$  are hydrogen, the third of  $R^3$ ,  $R^4$  and  $R^5$  is not methyl.

10

Alkyl  $R^1$  and  $R^2$  of formula III are suitably alkyl having up to 7 carbon atoms, preferably up to 4 carbon atoms. Thus, alkyl R may be methyl, ethyl, n-propyl, isopropyl, n-butyl or isobutyl.

15

Halogen  $R^1$  and  $R^2$  is chloro, bromo, fluoro, or iodo.

Alkoxy  $R^1$  and  $R^2$  are suitably alkoxy groups having up to 5 carbon atoms, preferably up to 3 carbon atoms, as methoxy, ethoxy, n-propoxy, or isopropoxy.

20

Alkanoyl  $R^1$  and  $R^2$  have preferably up to 4 carbon atoms and are e.g. formyl, acetyl, or propionyl, preferably acetyl.

25

A preferred group of compounds of the general formula III are those wherein  $R^1$  and  $R^2$  are the same or different and are each selected from the group consisting of hydrogen, alkyl, carbomethoxy, alkoxy, and alkanoyl, whereby  $R^1$  and  $R^2$  are not both hydrogen,  $R^6$  is hydrogen, and  $R^3$ ,  $R^4$ , and  $R^5$  are the same or different and are each selected from the group consisting of hydrogen, methyl, methoxy, and ethoxy, whereby  $R^3$ ,  $R^4$ , and  $R^5$  are not all hydrogen, and whereby when two of  $R^3$ ,  $R^4$ , and  $R^5$  are hydrogen the third of  $R^3$ ,  $R^4$ , and  $R^5$  is not methyl.

30

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A second preferred group of compounds of the general formula III are those wherein  $R^1$  and  $R^2$  are the same or different and are each selected from the group consisting of hydrogen, alkyl, halogen, carbomethoxy, carbethoxy, alkoxy, and alkanoyl, 5  $R^6$  is selected from the group consisting of hydrogen, methyl, and ethyl,  $R^3$  is methyl,  $R^4$  is methoxy, and  $R^5$  is methyl.

A third preferred group of compounds of the general formula III are those wherein  $R^1$  and  $R^2$  are the same or different 10 and are each selected from the group consisting of hydrogen, alkyl, halogen, carbomethoxy, carbethoxy, alkoxy and alkanoyl,  $R^6$  is selected from the group consisting of hydrogen, methyl and ethyl, and  $R^3$  is hydrogen,  $R^4$  is methoxy and  $R^5$  is methyl or  $R^3$  is methyl,  $R^4$  is methoxy and  $R^5$  is hydrogen.

15 A fourth preferred group of compounds of the general formula III are those wherein  $R^1$  and  $R^2$  are the same or different and are each selected from the group consisting of hydrogen, alkyl, halogen, carbomethoxy, carbethoxy, alkoxy, and alkanoyl, 20  $R^6$  is selected from the group consisting of hydrogen, methyl and ethyl,  $R^3$  and  $R^5$  are hydrogen and  $R^4$  is methoxy.

A fifth preferred group of compounds of the general formula III are those wherein  $R^1$  and  $R^2$  are the same or different 25 and are each selected from the group consisting of hydrogen, alkyl, halogen, carbomethoxy, carbethoxy, alkoxy, and alkanoyl,  $R^6$  is selected from the group consisting of hydrogen, methyl and ethyl, and  $R^3$  and  $R^5$  are methyl and  $R^4$  is hydrogen.

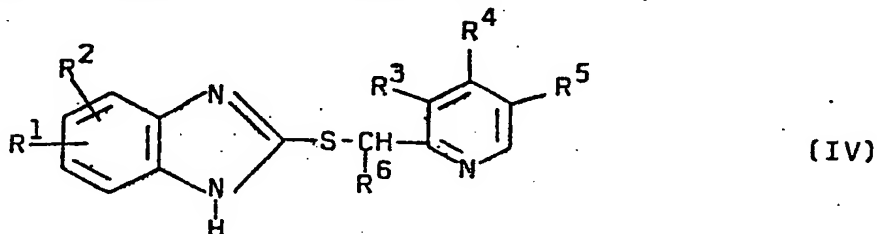
30 A sixth preferred group of compounds of the general formula III are those wherein  $R^1$  and  $R^2$  are the same or different and are each selected from the group consisting of hydrogen, alkyl, halogen, carbomethoxy, carbethoxy, alkoxy, and alkanoyl,  $R^6$  is selected from the group consisting of hydrogen, methyl 35 and ethyl,  $R^3$  and  $R^5$  are hydrogen and  $R^4$  is ethoxy, methoxy-ethoxy or ethoxyethoxy.

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A seventh preferred group of compounds of the general formula III are those wherein  $R^1$  and  $R^2$  are the same or different and are each selected from the group consisting of hydrogen, alkyl, halogen, carbomethoxy, alkoxy, and alkanoyl,  $R^6$  is selected from the group consisting of hydrogen, methyl, and ethyl,  $R^3$ ,  $R^4$ , and  $R^5$  are all methyl.

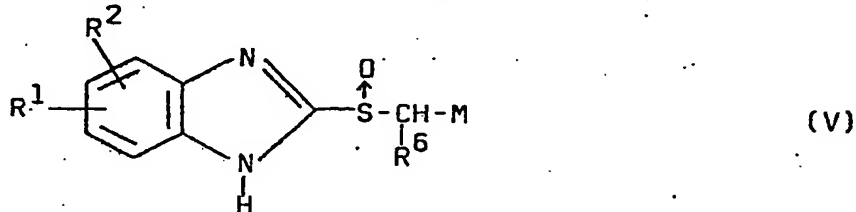
Compounds of formula III above may be prepared according to the following methods:

a) oxidizing a compound of formula IV

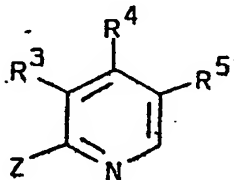


wherein  $R^1$ ,  $R^2$ ,  $R^6$ ,  $R^3$ ,  $R^4$ , and  $R^5$  have the meanings given, to the formation of a compound of formula III.

b) reacting a compound of the formula V



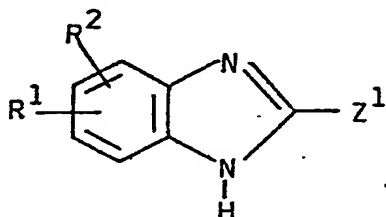
wherein  $R^1$ ,  $R^2$ , and  $R^6$  have the meanings given above and M is a metal selected from the group consisting of K, Na and Li, with a compound of formula VI.



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wherein  $R^3$ ,  $R^4$ , and  $R^5$  have the same meanings as given above, Z is a reactive esterified hydroxy group, to the formation of a compound of formula III;

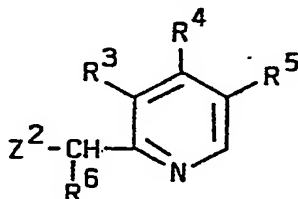
5 c) reacting a compound of the formula VII



(VII)

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wherein  $R^1$ , and  $R^2$  have the same meanings as given above and  $Z^1$  is SH or a reactive esterified hydroxy group, with  
15 a compound of the formula VIII

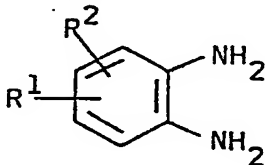


(VIII)

20

wherein  $R^6$ ,  $R^3$ ,  $R^4$ , and  $R^5$  have the same meanings as given above, and  $Z^2$  is a reactive esterified hydroxy group or SH, to the formation of an intermediate of formula IV above,  
25 which then is oxidized to give a compound of formula III;

d) reacting a compound of the formula IX



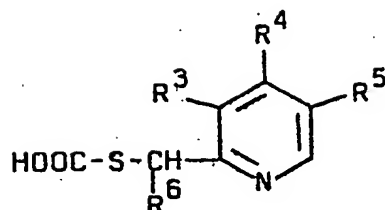
(IX)

30

wherein  $R^1$  and  $R^2$  have the same meanings as given above with a compound of the formula X  
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(X)



5

wherein R<sup>6</sup>, R<sup>3</sup>, R<sup>4</sup>, and R<sup>5</sup> have the same meanings as given above, to the formation of an intermediate of formula IV above, which then is oxidized to give a compound of formula  
 10 III, which compound may be converted to its therapeutically acceptable salts, if so desired.

In the reactions above, Z, Z<sup>1</sup>, and Z<sup>2</sup> may be a reactive, esterified hydroxy group which is a hydroxy group esterified  
 15 with strong, inorganic or organic acid, preferably a hydrohalogen acid, such as hydrochloric acid, hydrobromic acid, or hydroiodic acid, also sulfuric acid or a strong organic sulfonic acid as a strong aromatic acid, e.g. benzene-  
 20 sulfonic acid, 4-bromobenzenesulfonic acid or 4-toluene-sulfonic acid.

The oxidation of the sulfur atom in the chains above to sulfinyl (S→O) takes place in the presence of an oxidizing agent selected from the group consisting of nitric acid,  
 25 hydrogen peroxide, peracids, peresters, ozone, dinitrogen-tetraoxide, iodosobenzene, N-halosuccinimide, 1-chlorobenzo-triazole, t-butylhypochlorite, diazobicyclo-[2,2,2]-octane bromine complex, sodium metaperiodate, selenium dioxide, manganese dioxide, chromic acid, ceric ammonium nitrate,  
 30 bromine, chlorine, and sulfuryl chloride. The oxidation usually takes place in a solvent wherein the oxidizing agent is present in some excess in relation to the product to be oxidized.

35 Depending on the process conditions and the starting materials, the end product is obtained either as the free base or in the acid addition salt, both of which are included within the scope of the invention. Thus, basic, neutral or or mixed salts may be obtained as well as hemi, mono, sesqui



or polyhydrates. The acid addition salts of the new compounds may in a manner known per se be transformed into free base using basic agents such as alkali or by ion exchange. On the other hand, the free bases obtained may  
5 form salts with organic or inorganic acids. In the preparation of acid addition salts preferably such acids are used which form suitable therapeutically acceptable salts. Such acids include hydrohalogen acids, sulfonic, phosphoric, nitric, and perchloric acids; aliphatic, alicyclic, aromatic,  
10 heterocyclic carboxy or sulfonic acids, such as formic, acetic, propionic, succinic, glycolic, lactic, malic, tartaric, citric, ascorbic, maleic, hydroxymaleic, pyruvic, phenylacetic, benzoic, p-aminobenzoic, antranilic, p-hydroxybenzoic, salicylic or p-aminosalicylic acid,  
15 embonic, methanesulfonic, ethanesulfonic, hydroxyethanesulfonic, ethylenesulfonic, halogenbenzenesulfonic, toluenesulfonic, naphtylsulfonic or sulfanilic acids; methionine, tryptophane, lysine or arginine.

20 These or other salts of the new compounds, as e.g. picrates, may serve as purifying agents of the free bases obtained. Salts of the bases may be formed, separated from solution, and then the free base can be recovered from a new salt solution in a purer state. Because of the relationship  
25 between the new compounds in free base form and their salts, it will be understood that the corresponding salts are included within the scope of the invention.

Some of the new compounds may, depending on the choice of  
30 starting materials and process, be present as optical isomers or racemate, or if they contain at least two asymmetric carbon atoms, be present as an isomer mixture (racemate mixture).

35 The isomer mixtures (racemate mixtures) obtained may be separated into two stereoisomeric (diastereomeric) pure racemates by means of chromatography or fractional crystal-

lization.

The racemates obtained can be separated according to known methods, e.g. recrystallization from an optically active solvent, use of microorganisms, reactions with optically active acids forming salts which can be separated, separation based on different solubilities of the diastereomers. Suitable optically active acids are the L- and D-forms of tartaric acid, di-o-tolyl-tartaric acid, malic acid, mandelic acid, camphorsulfonic acid or quinic acid. Preferably the more active part of the two antipodes is isolated.

The starting materials are known or may, if they should be new, be obtained according to processes known per se.

In clinical use the compounds of the invention are administered orally, rectally or by injection in the form of a pharmaceutical preparation which contains an active component either as a free base or as a pharmaceutically acceptable, non-toxic acid addition salt, such as hydrochloride, lactate, acetate, sulfamate, in combination with a pharmaceutically acceptable carrier. The carrier may be in the form of a solid, semisolid or liquid diluent, or a capsule. These pharmaceutical preparations are a further object of the invention. Usually the amount of active compound is between 0.1 to 95 % by weight of the preparation, between 0.5 to 20 % by weight in preparations for injection and between 2 and 50 % by weight in preparations for oral administration.

In the preparation of pharmaceutical preparations containing a compound of the present invention in the form of dosage units for oral administration the compound selected may be mixed with a solid, pulverulent carrier, such as lactose, saccharose, sorbitol, mannitol, starch, amylopectin, cellulose derivatives or gelatin, as well as with an anti-friction agent such as magnesium stearate, calcium stearate, and polyethyleneglycol waxes. The mixture is then pressed

into tablets. If coated tablets are desired, the above prepared core may be coated with a concentrated solution of sugar, which may contain gum arabic, gelatin, talc, titanium dioxide or with a lacquer dissolved in volatile organic solvent or mixture of solvents. To this coating various dyes may be added in order to distinguish among tablets with different active compounds or with different amounts of the active compound present.

- 10 Soft gelatin capsules may be prepared which capsules contain a mixture of the active compound or compounds of the invention and vegetable oil. Hard gelatin capsules may contain granules of the active compound in combination with a solid, pulverulent carrier as lactose, saccharose, sorbitol, mannitol, potato starch, corn starch, amylopectin, cellulose derivatives or gelatin.

Dosage units for rectal administration may be prepared in the form of suppositories which contain the active substance in a mixture with a neutral fat base, or they may be prepared in the form of gelatin-rectal capsules which contain the active substance in a mixture with a vegetable oil or paraffin oil.

- 25 Liquid preparations for oral administration may be prepared in the form of syrups or suspensions, e.g. solutions containing from 0.2 % to 20 % by weight of the active ingredient and the remainder consisting of sugar and a mixture of ethanol, water, glycerol and propylene glycol. If desired, such liquid preparations may contain colouring agents, flavouring agents, saccharin and carboxymethylcellulose as a thickening agent.

- 35 Solutions for parenteral administration by injection may be prepared as an aqueous solution of a watersoluble pharmaceutically acceptable salt of the active compound, preferably in a concentration from 0.5 % to 10 % by weight. These solutions may also contain stabilizing agents and/or

buffering agents and may be manufactured in different dosage unit ampoules.

Pharmaceutical tablets for oral use are prepared in the following manner: The solid substances are ground or sieved to a certain particle size, and the binding agent is homogenized and suspended in a suitable solvent. The therapeutically active compounds and auxiliary agents are mixed with the binding agent solution. The resulting mixture is moistened to form a uniform suspension having the consistency of wet snow. The moistening causes the particles to aggregate slightly, and the resulting mass is pressed through a stainless steel sieve having a mesh size of approximately 1 mm. The layers of the mixture are dried in carefully controlled drying cabinets for approximately ten hours to obtain the desired particle size and consistency. The granules of the dried mixture are sieved to remove any powder. To this mixture, disintegrating, antifriction and antiadhesive agents are added. Finally, the mixture is pressed into tablets using a machine with the appropriate punches and dies to obtain the desired tablet size. The pressure applied affects the size of the tablet, its strength and its ability to dissolve in water. The compression pressure used should be in the range 0.5 to 5 tons. Tablets are manufactured at the rate of 20.000 to 200.000 per hour. The tablets, especially those which are rough or bitter, may be coated with a layer of sugar or some other palatable substance. They are then packaged by machines having electronic counting devices. The different types of packages consist of glass or plastic gallipots, boxes, tubes and specific dosage adapted packages.

The typical daily dose of the active substance varies according to the individual needs and the manner of administration. In general, oral dosages range from 100 to 400 mg/day of active substance and intravenous dosages range from 5 to 20 mg/day.

The following illustrates a preferred embodiment of the invention without being limited thereto. Temperature is given in degrees Centigrade.

- 5 The starting materials in the examples found below were prepared in accordance with the following methods:
- (1) a 1,2-diamino compound, such as o-phenylenediamine was reacted with potassium ethylxanthate (according to Org. Synth. Vol. 30, p. 56) to form a 2-mercaptobenzimidazole;
  - 10 (2) the compound 2-chloromethylpyridine was prepared by reacting 2-hydroxymethylpyridine with thionylchloride (according to Arch. Pharm. Vol. 26, pp. 448-451 (1956));
  - (3) the compound 2-chloromethylbenzimidazole was prepared by condensing o-phenylenediamine with chloroacetic acid.

15

#### Example 1

- 28.9 g of 2-[2-(4,5-dimethyl)pyridylmethylthio]-(5-acetyl-6-methyl)-benzimidazole were dissolved in 160 ml of  $\text{CHCl}_3$ ,
- 20 24.4 g of m-chloroperbenzoic acid were added in portions while stirring and cooling to  $5^\circ\text{C}$ . After 10 minutes, the precipitated m-chlorobenzoic acid was filtered off. The filtrate was diluted with  $\text{CH}_2\text{Cl}_2$ , washed with  $\text{Na}_2\text{CO}_3$  solution, dried over  $\text{Na}_2\text{SO}_4$  and evaporated in vacuo. The residue
- 25 crystallized when diluted with  $\text{CH}_3\text{CN}$ , and 2-[2-(4,5-dimethyl)pyridylmethyldisulfinyl]-(5-acetyl-6-methyl)benzimidazole was recrystallized from  $\text{CH}_3\text{CN}$ . Yield 22.3 g; m.p.  $158^\circ\text{C}$ .

#### 30 Examples 2-30

- The preparation of compounds of formula III labelled 2-26 was carried out in accordance with Example 1 above. The compounds prepared are listed in Table I which identifies
- 35 the substituents for these compounds.

Example 31 (method c)

- 0.1 moles of 4-6-dimethyl-2-mercaptobenzimidazole were dissolved in 20 ml of water and 200 ml of ethanol containing 0.2 moles of sodium hydroxide. 0.1 moles of 2-chloromethyl-(3,5-dimethyl)pyridine hydrochloride were added and the mixture was refluxed for two hours. The sodium chloride formed was filtered off and the solution was evaporated in vacuo. The residue was dissolved in acetone and was treated with active carbon. An equivalent amount of concentrated hydrochloric acid was added, whereupon the mono-hydrochloride of 2-[2-(3,5-dimethyl)pyridylmethylthio]-(4,6-dimethyl)benzimidazole was isolated. Yield 0.05 moles.
- This compound was then oxidized in accordance with Example 1 above to give the corresponding sulfinyl compound melting point 50-55°C.

Example 32 (method b)

- 0.1 moles of 2-[Li-methylsulfinyl](5-acetyl-6-methyl)benzimidazole were dissolved in 150 mls of benzene. 0.1 moles 2-chloro-(3,5-dimethyl)pyridine were added and the mixture was refluxed for two hours. The lithiumchloride formed was filtered off, and the solution was evaporated in vacuo. The residue was crystallized from CH<sub>3</sub>CN, and recrystallized from the same solvent. Yield 0.82 moles of 2-[2-(3,5-dimethyl)pyridylmethylsulfinyl]-(5-acetyl-6-methyl)benzimidazole melting at 171°C.

Example 33 (method d)

- 23.4 g of 2-[2-(3,4,5-trimethyl)pyridylmethylthio]formic acid and 16.6 g of o-(5-acetyl-6-methyl)phenylenediamine were boiled for 40 minutes in 100 ml of 4N HCl. The mixture was cooled and neutralized with ammonia. The neutral solution was then extracted with ethyl acetate. The organic phase was

treated with active carbon and evaporated in vacuo. The residue was dissolved in acetone whereupon an equivalent of concentrated HCl was added. The precipitated hydrochloride was filtered off after cooling and the salt was  
5 recrystallized from absolute ethanol and some ether. Yield of 2-[2-(3,4,5-trimethylpyridyl)methylthio]-(5-acetyl-6-methyl)benzimidazole was 6.5 g.

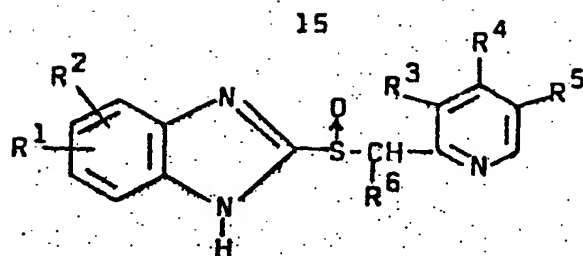
This compound was then oxidized in accordance with Example 1  
10 above, to give the corresponding sulfinyl derivative.  
M.p. 190°C.

Example 34 (method c)

15 22.0 g of 2-mercapto-(5-acetyl-6-methyl)benzimidazole and 19.5 g of chloromethyl(4,5-dimethyl)pyridine hydrochloride were dissolved in 200 ml of 95 % ethanol. 8 g of sodium hydroxide in 20 ml of water were added, whereupon the solution was refluxed for two hours. The sodium chloride formed  
20 was filtered off and the solution was evaporated in vacuo. The residue, 2-[2-(4,5-dimethyl)pyridylmethylthio]-(5-acetyl-6-methyl)benzimidazole, was recrystallized from 70 % ethanol. Yield 10.6 g.

25 This compound was then oxidized in accordance with Example 1 above, to give the corresponding sulfinyl derivative.  
M.p. 158°C.

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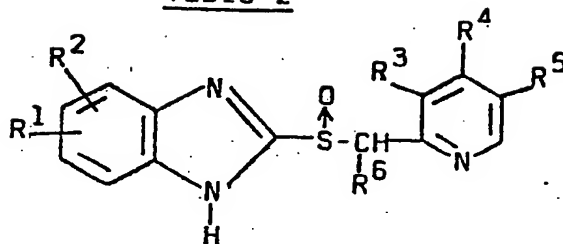
Ex.	R <sup>1</sup>	R <sup>2</sup>	R <sup>6</sup>	R <sup>3</sup>	R <sup>4</sup>	R <sup>5</sup>	M.p. °C
1	5-COCH <sub>3</sub>	6-CH <sub>3</sub>	H	H	CH <sub>3</sub>	CH <sub>3</sub>	158
2	5-COOCH <sub>3</sub>	6-CH <sub>3</sub>	H	H	CH <sub>3</sub>	CH <sub>3</sub>	163
3	5-COOCH <sub>3</sub>	H	H	H	CH <sub>3</sub>	CH <sub>3</sub>	141
4	5-COCH <sub>3</sub>	6-CH <sub>3</sub>	H	CH <sub>3</sub>	CH <sub>3</sub>	H	160
5	5-COOCH <sub>3</sub>	6-CH <sub>3</sub>	H	CH <sub>3</sub>	CH <sub>3</sub>	H	163
6	4-CH <sub>3</sub>	6-CH <sub>3</sub>	H	CH <sub>3</sub>	H	CH <sub>3</sub>	50-55
7	5-COCH <sub>3</sub>	6-CH <sub>3</sub>	H	CH <sub>3</sub>	H	CH <sub>3</sub>	171
8	5-COCH <sub>3</sub>	6-CH <sub>3</sub>	H	CH <sub>3</sub>	CH <sub>3</sub>	CH <sub>3</sub>	190
9	5-COCH <sub>3</sub>	6-CH <sub>3</sub>	H	H	OCH <sub>3</sub>	H	165
10	4-CH <sub>3</sub>	6-CH <sub>3</sub>	H	H	OCH <sub>3</sub>	H	122
11	5-COCH <sub>3</sub>	6-CH <sub>3</sub>	H	CH <sub>3</sub>	OCH <sub>3</sub>	CH <sub>3</sub>	156
12	5-COOCH <sub>3</sub>	6-CH <sub>3</sub>	H	CH <sub>3</sub>	H	CH <sub>3</sub>	144
13	5-COOCH <sub>3</sub>	6-CH <sub>3</sub>	H	CH <sub>3</sub>	CH <sub>3</sub>	CH <sub>3</sub>	185
14	5-COOCH <sub>3</sub>	6-CH <sub>3</sub>	H	H	OCH <sub>3</sub>	H	169
15	5-COOCH <sub>3</sub>	6-CH <sub>3</sub>	H	H	OC <sub>2</sub> H <sub>5</sub>	H	148
16	5-COOCH <sub>3</sub>	6-CH <sub>3</sub>	H	CH <sub>3</sub>	OCH <sub>3</sub>	H	175
17	5-COOCH <sub>3</sub>	6-CH <sub>3</sub>	H	CH <sub>3</sub>	OCH <sub>3</sub>	CH <sub>3</sub>	155
18	5-COOCH <sub>3</sub>	6-CH <sub>3</sub>	H	H	OCH <sub>3</sub>	CH <sub>3</sub>	158
19	5-COOCH <sub>3</sub>	H	H	CH <sub>3</sub>	H	CH <sub>3</sub>	141
20	5-COOCH <sub>3</sub>	H	H	CH <sub>3</sub>	OCH <sub>3</sub>	CH <sub>3</sub>	142
21	5-COCH <sub>3</sub>	H	H	CH <sub>3</sub>	OCH <sub>3</sub>	CH <sub>3</sub>	162
22	5-OCH <sub>3</sub>	H	H	H	OCH <sub>3</sub>	CH <sub>3</sub>	178
23	5-OCH <sub>3</sub>	H	H	CH <sub>3</sub>	OCH <sub>3</sub>	CH <sub>3</sub>	156
24	5-CH <sub>3</sub>	H	H	CH <sub>3</sub>	OCH <sub>3</sub>	CH <sub>3</sub>	181
25	H	H	H	CH <sub>3</sub>	OCH <sub>3</sub>	CH <sub>3</sub>	165
26	5-Cl	H	H	CH <sub>3</sub>	OCH <sub>3</sub>	CH <sub>3</sub>	185
27	5-CH <sub>3</sub>	H	H	H	OC <sub>2</sub> H <sub>4</sub> OCH <sub>3</sub>	H	119
28	5-COOC <sub>2</sub> H <sub>5</sub>	H	H	CH <sub>3</sub>	OCH <sub>3</sub>	CH <sub>3</sub>	150-5
29	5-COOCH <sub>3</sub>	H	CH <sub>3</sub>	CH <sub>3</sub>	H	CH <sub>3</sub>	130
30	5-CH <sub>3</sub>	H	CH <sub>3</sub>	CH <sub>3</sub>	H	CH <sub>3</sub>	152



Biological effect

- The compounds of the invention possess worthwhile therapeutic properties as gastric acid secretion inhibitors as demonstrated by the following tests. To determine the gastric acid secretion inhibitory properties, experiments have been performed on conscious dogs provided with gastric fistulas of conventional type and duodenal fistulas, the latter ones used for direct intraduodenal administration of the test compounds. After 18 hours starvation and deprivation of water the dogs were given a subcutaneous infusion of pentagastrin (1-4 nmol/kg, h) lasting for 6-7 hours. Gastric juice was collected in consecutive 30 minutes samples. An aliquot of each sample was titrated with 0.1 N NaOH to pH 7.0 for titrable acid concentration using an automatic titrator and pH-meter (Radiometer, Copenhagen, Denmark). Acid output was calculated as mmol  $H^+$ /60 minutes. The percent inhibition compared to control experiments was calculated for each compound and the peak inhibitory effect is given in Table 2 below. The test compounds, -suspended in 0.5 % Methocel<sup>®</sup> (methyl cellulose), were given intraduodenally in doses from 4-20  $\mu$ mol/kg when the secretory response to pentagastrin has reached a steady level.
- In the test prior known compounds were compared with the compounds of the present invention as will be evident from the Table 2 below.
- The following gastric acid inhibiting effect data were obtained for a number of compounds tested according to the method described.

Table 2



	Ex.	R <sup>1</sup>	R <sup>2</sup>	R <sup>6</sup>	R <sup>3</sup>	R <sup>4</sup>	R <sup>5</sup>	Dose μmol/kg	Effect % inhibition
10	1	5-COCH <sub>3</sub>	6-CH <sub>3</sub>	H	H	CH <sub>3</sub>	CH <sub>3</sub>	2	90
	4	5-COCH <sub>3</sub>	6-CH <sub>3</sub>	H	CH <sub>3</sub>	CH <sub>3</sub>	H	1	60
	7	5-COCH <sub>3</sub>	6-CH <sub>3</sub>	H	CH <sub>3</sub>	H	CH <sub>3</sub>	2	100
	8	5-COCH <sub>3</sub>	6-CH <sub>3</sub>	H	CH <sub>3</sub>	CH <sub>3</sub>	CH <sub>3</sub>	4	100
15	9	5-COCH <sub>3</sub>	6-CH <sub>3</sub>	H	H	OCH <sub>3</sub>	H	2	95
	11	5-COCH <sub>3</sub>	6-CH <sub>3</sub>	H	CH <sub>3</sub>	OCH <sub>3</sub>	CH <sub>3</sub>	0.5	70
	x	5-COCH <sub>3</sub>	6-CH <sub>3</sub>	H	H	CH <sub>3</sub>	H	20	30
	x	5-COCH <sub>3</sub>	6-CH <sub>3</sub>	H	H	H	CH <sub>3</sub>	8	80
20	2	5-COOCH <sub>3</sub>	6-CH <sub>3</sub>	H	H	CH <sub>3</sub>	CH <sub>3</sub>	2	60
	5	5-COOCH <sub>3</sub>	6-CH <sub>3</sub>	H	CH <sub>3</sub>	CH <sub>3</sub>	H	2	90
	12	5-COOCH <sub>3</sub>	6-CH <sub>3</sub>	H	CH <sub>3</sub>	H	CH <sub>3</sub>	2	70
	13	5-COOCH <sub>3</sub>	6-CH <sub>3</sub>	H	CH <sub>3</sub>	CH <sub>3</sub>	CH <sub>3</sub>	4	80
	14	5-COOCH <sub>3</sub>	6-CH <sub>3</sub>	H	H	OCH <sub>3</sub>	H	2	100
25	15	5-COOCH <sub>3</sub>	6-CH <sub>3</sub>	H	H	OC <sub>2</sub> H <sub>5</sub>	H	4	75
	16	5-COOCH <sub>3</sub>	6-CH <sub>3</sub>	H	CH <sub>3</sub>	OCH <sub>3</sub>	H	0.5	65
	17	5-COOCH <sub>3</sub>	6-CH <sub>3</sub>	H	CH <sub>3</sub>	OCH <sub>3</sub>	CH <sub>3</sub>	0.5	90
	18	5-COOCH <sub>3</sub>	6-CH <sub>3</sub>	H	H	OCH <sub>3</sub>	CH <sub>3</sub>		
	x	5-COOCH <sub>3</sub>	6-CH <sub>3</sub>	H	H	H	CH <sub>3</sub>	4	50
30	x	5-COOCH <sub>3</sub>	6-CH <sub>3</sub>	H	Br	H	H	4	0
	6	4-CH <sub>3</sub>	6-CH <sub>3</sub>	H	CH <sub>3</sub>	H	CH <sub>3</sub>	4	40
	10	4-CH <sub>3</sub>	6-CH <sub>3</sub>	H	H	OCH <sub>3</sub>	H	2	40
	x	4-CH <sub>3</sub>	6-CH <sub>3</sub>	H	H	H	H	4	30
35	x	4-CH <sub>3</sub>	6-CH <sub>3</sub>	H	H	H	CH <sub>3</sub>	12	50

cont.

Ex	R <sup>1</sup>	R <sup>2</sup>	R <sup>6</sup>	R <sup>3</sup>	R <sup>4</sup>	R <sup>5</sup>	Dose μmol/kg	Effect % inhibition
3	5-COOCH <sub>3</sub>	H	H	H	CH <sub>3</sub>	CH <sub>3</sub>	4	100
19	5-COOCH <sub>3</sub>	H	H	CH <sub>3</sub>	H	CH <sub>3</sub>	2	60
5	20	5-COOCH <sub>3</sub>	H	H	CH <sub>3</sub>	OCH <sub>3</sub>	0.5	65
x	5-COOCH <sub>3</sub>	H	H	H	H	CH <sub>3</sub>	20	90
x	5-COOCH <sub>3</sub>	H	H	H	H	H	20	50
21	5-COCH <sub>3</sub>	H	H	CH <sub>3</sub>	OCH <sub>3</sub>	CH <sub>3</sub>	0.5	60
10	x	5-COCH <sub>3</sub>	H	H	H	C <sub>2</sub> H <sub>5</sub>	20	40
22	5-OCH <sub>3</sub>	H	H	H	OCH <sub>3</sub>	CH <sub>3</sub>		
23	5-OCH <sub>3</sub>	H	H	CH <sub>3</sub>	OCH <sub>3</sub>	CH <sub>3</sub>	0.5	65
x	5-OCH <sub>3</sub>	H	H	H	CH <sub>3</sub>	H	20	10
15	24	5-CH <sub>3</sub>	H	H	CH <sub>3</sub>	OCH <sub>3</sub>	0.5	50
x	5-CH <sub>3</sub>	H	H	H	H	CH <sub>3</sub>	4	50
25	H	H	H	CH <sub>3</sub>	OCH <sub>3</sub>	CH <sub>3</sub>	0.5	60
x	H	H	H	H	H	H	4	50
20	28	5-COOC <sub>2</sub> H <sub>5</sub>	H	H	CH <sub>3</sub>	OCH <sub>3</sub>	0.5	50
26	5-Cl	H	H	CH <sub>3</sub>	OCH <sub>3</sub>	CH <sub>3</sub>	0.5	25
27	5-CH <sub>3</sub>	H	H	H	OC <sub>2</sub> H <sub>4</sub> OCH <sub>3</sub>	H	0.5	30
29	5-COOCH <sub>3</sub>	H	CH <sub>3</sub>	CH <sub>3</sub>	H	CH <sub>3</sub>	0.5	40

x denotes a previously known compound

25

### Example 35

A syrup containing 2 % (weight per volume) of active substance was prepared from the following ingredients:

30

2-[2-(4,5-dimethylpyridyl)methylsulfinyl]-  
-(5-acetyl-6-methyl)benzimidazole · HCl

2.0 g

Saccharin

0.6 g

Sugar

30.0 g

35 Glycerin

5.0 g

Flavouring agent

0.1 g

Ethanol 96 %

10.0 ml

Distilled water (sufficient to obtain a final  
volume of 100 ml)

0005129

Sugar, saccharin and the acid addition salt were dissolved in 60 g of warm water. After cooling, glycerin and a solution of flavouring agents dissolved in ethanol were added. To the mixture water was added to obtain a final volume of 100 ml.

The above given active substance may be replaced with other pharmaceutically acceptable acid addition salts.

10 Example 36

2-[2-(3,4-dimethyl)pyridylmethylsulfinyl]-(5-acetyl-6-methyl)benzimidazole · HCl (250 g) was mixed with lactose (175.8 g), potato starch (169.7 g) and colloidal silicic acid (32 g). The mixture was moistened with 10 % solution of gelatin and was ground through a 12-mesh sieve. After drying, potato starch (160 g), talc (50 g) and magnesium stearate (5 g) were added and the mixture thus obtained was pressed into tablets (10.000), with each tablet containing 25 mg of active substance. Tablets can be prepared that contain any desired amount of the active ingredient.

Example 37

25 Granules were prepared from 2-[2-(3,5-dimethyl)pyridylmethylsulfinyl]-(5-acetyl-6-methyl)benzimidazole-p-hydroxybenzoate (250 g), lactose (175.9 g) and an alcoholic solution of polyvinylpyrrolidone (25 g). After drying, the granules were mixed with talc (25 g), potato starch (40 g), and magnesium stearate (2.50 g) and were pressed into 10.000 tablets. These tablets are first coated with a 10 % alcoholic solution of shellac and thereupon with an aqueous solution containing saccharose (45 %), gum arabic (5 %), gelatin (4 %), and dyestuff (0.2 %). Talc and powdered sugar were used for powdering after the first five coatings. The coating was then covered with a 66 % sugar syrup and polished with a solution of 10 % carnauba wax in carbon tetrachloride.

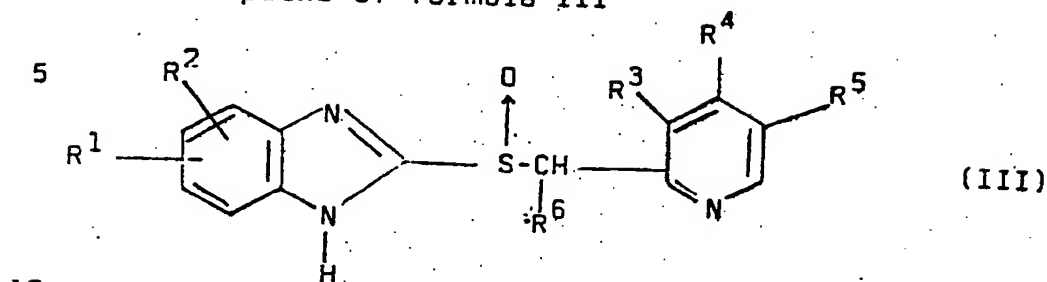
Example 38

2-[2-(3,5-dimethyl)pyridylmethylsulfinyl]-(5-acetyl-6-methyl)benzimidazole hydrochloride (1 g), sodium chloride  
5 (0.6 g) and ascorbic acid (0.1 g) were dissolved in sufficient amount of distilled water to give 100 ml of solution. This solution, which contains 10 mg of active substance for each ml, was used in filling ampoules, which were sterilized by heating at 120°C for 20 minutes.

Claims

0005129

1. A compound of formula III



or a therapeutically acceptable salt thereof in which  
 $R^1$  and  $R^2$  are the same or different and are selected  
 15 from the group consisting of hydrogen, alkyl, halogen, carbomethoxy, carbethoxy, alkoxy, and alkanoyl in any position,  $R^6$  is selected from the group consisting of hydrogen, methyl and ethyl,  $R^3$ ,  $R^4$ , and  $R^5$  are the same or different and are each selected from the group  
 20 consisting of hydrogen, methyl, methoxy, ethoxy, methoxy-ethoxy and ethoxy-ethoxy whereby  $R^3$ ,  $R^4$ , and  $R^5$  are not all hydrogen, and whereby when two of  $R^3$ ,  $R^4$ , and  $R^5$  are hydrogen, the third of  $R^3$ ,  $R^4$ , and  $R^5$  is not methyl.

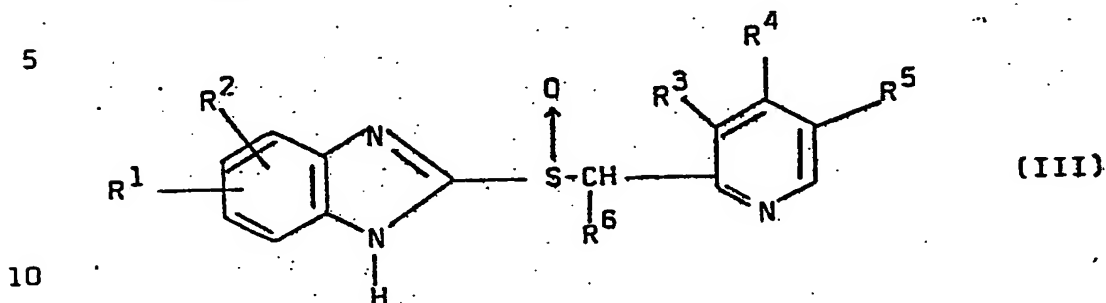
25 2. A compound according to claim 1, wherein  $R^1$  and  $R^2$  are same or different and are each selected from the group consisting of hydrogen, alkyl, carbomethoxy, alkoxy, and alkanoyl in any position, whereby  $R^1$  and  
 30  $R^2$  are not both hydrogen,  $R^6$  is hydrogen, and  $R^3$ ,  $R^4$ , and  $R^5$  are the same or different and are each selected from the group consisting of hydrogen, methyl, methoxy, and ethoxy, whereby  $R^3$ ,  $R^4$ , and  $R^5$  are not all hydrogen and whereby when two of  $R^3$ ,  $R^4$ , and  $R^5$  are hydrogen,  
 35 the third of  $R^3$ ,  $R^4$ , and  $R^5$  are not methyl.

3. A compound according to claim 1, wherein  $R^1$ ,  $R^2$ , and  $R^6$  have the meanings given and  $R^3$  and  $R^5$  are methyl and  $R^4$  is methoxy.
- 5 4. A compound according to claim 1, wherein  $R^1$ ,  $R^2$ , and  $R^6$  have the meanings given,  $R^4$  is methoxy, and  $R^3$  is hydrogen and  $R^5$  is methyl, or  $R^5$  is hydrogen and  $R^3$  is methyl.
- 10 5. A compound according to claim 1 or a therapeutically acceptable salt thereof in which  $R^1$ ,  $R^2$ , and  $R^6$  have the meanings given,  $R^3$  and  $R^5$  are hydrogen, and  $R^4$  is methoxy, ethoxy, methoxyethoxy or ethoxy-ethoxy.
- 15 6. A compound according to claim 1 or a therapeutically acceptable salt thereof in which  $R^1$ ,  $R^2$ , and  $R^6$  have the meanings given, and  $R^3$ , and  $R^5$  are methyl and  $R^4$  is hydrogen.
- 20 7. A compound according to claim 1 and selected from the group consisting of
- 2-[2-(3,4-dimethyl)-pyridylmethylsulfinyl]-(5-acetyl-6-methyl)-benzimidazole,
- 2-[2-(3,5-dimethyl)-pyridylmethylsulfinyl]-(4,6-dimethyl)-  
25 -benzimidazole,
- 2-[2-(4,5-dimethyl)-pyridylmethylsulfinyl]-(5-carbomethoxy)-benzimidazole,
- 2-[2-(4,5-dimethyl)-pyridylmethylsulfinyl]-(5-acetyl-6-methyl)-benzimidazole,
- 30 2-[2-(4,5-dimethyl)-pyridylmethylsulfinyl]-(5-carbomethoxy-6-methyl)-benzimidazole,
- 2-[2-(3,4-dimethyl)-pyridylmethylsulfinyl]-(5-carbomethoxy-6-methyl)-benzimidazole,
- 2-[2-(3,5-dimethyl)-pyridylmethylsulfinyl]-(5-acetyl-6-methyl)-benzimidazole,
- 35 2-[2-(3,4,5-trimethyl)-pyridylmethylsulfinyl]-(5-acetyl-6-methyl)-benzimidazole,

- 5 2-[2-(4-methoxy)-pyridylmethylsulfinyl]-(5-acetyl-6-methyl)-  
-benzimidazole  
2-[2-(4-methoxy)-pyridylmethylsulfinyl]-(4,6-dimethyl)-  
-benzimidazole  
2-[2-(3,5-dimethyl-4-methoxy)-pyridylmethylsulfinyl]-(5-  
10 acetyl-6-methyl)-benzimidazole,  
2-[2-(3,5-dimethyl)-pyridylmethylsulfinyl]-(5-carbomethoxy-  
-6-methyl)-benzimidazole,  
2-[2-(3,4,5-trimethyl)-pyridylmethylsulfinyl]-(5-carbomethoxy-  
-6-methyl)-benzimidazole,  
15 2-[2-(4-methoxy)-pyridylmethylsulfinyl]-(5-carbomethoxy-6-  
methyl)-benzimidazole,  
2-[2-(4-ethoxy)-pyridylmethylsulfinyl]-(5-carbomethoxy-6-  
methyl)-benzimidazole,  
2-[2-(3-methyl-4-methoxy)-pyridylmethylsulfinyl]-(5-carbo-  
20 methoxy-6-methyl)-benzimidazole,  
2-[2-(3,5-dimethyl-4-methoxy)-pyridylmethylsulfinyl]-(5-carbo-  
methoxy-6-methyl)-benzimidazole,  
2-[2-(4-methoxy-5-methyl)-pyridylmethylsulfinyl]-(5-carbo-  
methoxy-6-methyl)-benzimidazole,  
25 2-[2-(3,5-dimethyl)-pyridylmethylsulfinyl]-(5-carbomethoxy)-  
-benzimidazole,  
2-[2-(3,5-dimethyl-4-methoxy)-pyridylmethylsulfinyl]-(5-carbo-  
methoxy)-benzimidazole,  
2-[2-(3,5-dimethyl-4-methoxy)-pyridylmethylsulfinyl]-(5-  
30 acetyl)-benzimidazole,  
2-[2-(4-methoxy-5-methyl)-pyridylmethylsulfinyl]-(5-methoxy)-  
-benzimidazole,  
2-[2-(3,5-dimethyl-4-methoxy)-pyridylmethylsulfinyl]-(5-  
-methoxy)-benzimidazole,  
35 2-[2-(3,5-dimethyl-4-methoxy)-pyridylmethylsulfinyl]-(5-  
methyl)-benzimidazole,  
2-[2-(3,5-dimethyl-4-methoxy)-pyridylmethylsulfinyl]-benzi-  
midazole,  
2-[2-(3,5-dimethyl-4-methoxy)-pyridylmethylsulfinyl]-(5-  
40 chloro)-benzimidazole



8. A pharmaceutical preparation for inhibiting gastric acid secretion, characterized in that it contains as active agent a compound of formula III



or a pharmaceutically acceptable non-toxic acid addition salt thereof in a therapeutically effective amount in which  $R^1$  and  $R^2$  are the same or different and are selected from the group consisting of hydrogen, alkyl, halogen, carbomethoxy, carbethoxy, alkoxy, and alkanoyl in any position,  $R^6$  is selected from the group consisting of hydrogen, methyl, and ethyl  $R^3$ ,  $R^4$ , and  $R^5$  are the same or different and are each selected from the group consisting of hydrogen, methyl, methoxy, ethoxy, methoxy-ethoxy, and ethoxy-ethoxy whereby  $R^3$ ,  $R^4$ , and  $R^5$  are not all hydrogen, and whereby when two of  $R^3$ ,  $R^4$ , and  $R^5$  are hydrogen, the third of  $R^3$ ,  $R^4$ , and  $R^5$  is not methyl.

9. A pharmaceutical preparation according to claim 8 wherein the active ingredient is selected from the group consisting of

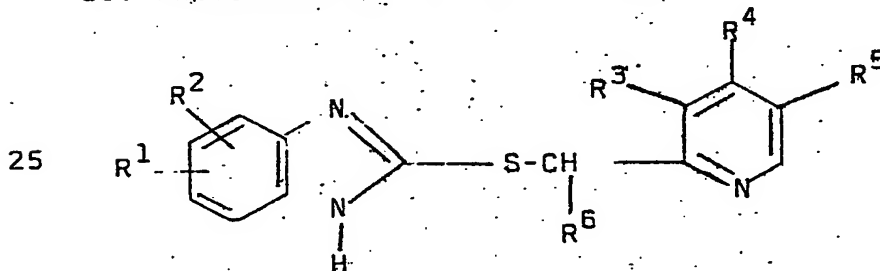
- 2-[2-(3,4-dimethyl)-pyridylmethylsulfinyl]-(5-acetyl-6-methyl)-benzimidazole,
- 2-[2-(3,5-dimethyl)-pyridylmethylsulfinyl]-(4,6-dimethyl)-benzimidazole,
- 5 2-[2-(4,5-dimethyl)-pyridylmethylsulfinyl]-(5-carbomethoxy)-benzimidazole,
- 2-[2-(4,5-dimethyl)-pyridylmethylsulfinyl]-(5-acetyl-6-methyl)-benzimidazole,
- 10 2-[2-(4,5-dimethyl)-pyridylmethylsulfinyl]-(5-carbomethoxy-6-methyl)-benzimidazole,
- 2-[2-(3,4-dimethyl)-pyridylmethylsulfinyl]-(5-carbomethoxy-6-methyl)-benzimidazole,
- 2-[2-(3,5-dimethyl)-pyridylmethylsulfinyl]-(5-acetyl-6-methyl)-benzimidazole,
- 15 2-[2-(3,4,5-trimethyl)-pyridylmethylsulfinyl]-(5-acetyl-6-methyl)-benzimidazole,
- 2-[2-(4-methoxy)-pyridylmethylsulfinyl]-(5-acetyl-6-methyl)-benzimidazole,
- 2-[2-(4-methoxy)-pyridylmethylsulfinyl]-(4,6-dimethyl)-benzimidazole,
- 20 2-[2-(3,5-dimethyl-4-methoxy)-pyridylmethylsulfinyl]-(5-acetyl-6-methyl)-benzimidazole,
- 2-[2-(3,5-dimethyl)-pyridylmethylsulfinyl]-(5-carbomethoxy-6-methyl)-benzimidazole,
- 25 2-[2-(3,4,5-trimethyl)-pyridylmethylsulfinyl]-(5-carbomethoxy-6-methyl)-benzimidazole,
- 2-[2-(4-methoxy)-pyridylmethylsulfinyl]-(5-carbomethoxy-6-methyl)-benzimidazole,
- 2-[2-(4-ethoxy)-pyridylmethylsulfinyl]-(5-carbomethoxy-6-methyl)-benzimidazole,
- 30 2-[2-(3-methyl-4-methoxy)-pyridylmethylsulfinyl]-(5-carbomethoxy-6-methyl)-benzimidazole,
- 2-[2-(3,5-dimethyl-4-methoxy)-pyridylmethylsulfinyl]-(5-carbomethoxy-6-methyl)-benzimidazole,
- 35 2-[2-(4-methoxy-5-methyl)-pyridylmethylsulfinyl]-(5-carbomethoxy-6-methyl)-benzimidazole,

- 2-[2-(3,5-dimethyl)-pyridylmethylsulfinyl]-(5-carbomethoxy)-benzimidazole,  
 2-[2-(3,5-dimethyl-4-methoxy)-pyridylmethylsulfinyl]-(5-carbomethoxy)-benzimidazole,  
 5 2-[2-(3,5-dimethyl-4-methoxy)-pyridylmethylsulfinyl]-(5-acetyl)-benzimidazole,  
 2-[2-(4-methoxy-5-methyl)-pyridylmethylsulfinyl]-(5-methoxy)-benzimidazole,  
 2-[2-(3,5-dimethyl-4-methoxy)-pyridylmethylsulfinyl]-(5-methoxy)-benzimidazole,  
 10 2-[2-(3,5-dimethyl-4-methoxy)-pyridylmethylsulfinyl]-(5-methyl)-benzimidazole,  
 2-[2-(3,5-dimethyl-4-methoxy)-pyridylmethylsulfinyl]-benzimidazole,  
 15 2-[2-(3,5-dimethyl-4-methoxy)-pyridylmethylsulfinyl]-(5-chloro)-benzimidazole,

or a pharmaceutically acceptable non-toxic addition salt thereof.

20

10. Intermediates of the formula



- 30 wherein  $R^1$  and  $R^2$ , preferably in 3 to 5 position, are the same or different and are selected from the group consisting of hydrogen, alkyl, halogen, carbomethoxy, carbethoxy, alkoxy and alkanoyl,  $R^6$  is selected from the group consisting of hydrogen, methyl, and ethyl, and  $R^3$ ,  $R^4$ ,  
 35 and  $R^5$  are the same or different and are selected from the group consisting of hydrogen, methyl, methoxy, ethoxy, methoxy-ethoxy, and ethoxy-ethoxy whereby  $R^3$ ,  $R^4$ , and  $R^5$

are not all hydrogen when two of  $R^3$ ,  $R^4$ , and  $R^5$  are hydrogen, the third of  $R^3$ ,  $R^4$ , and  $R^5$  is not methyl.



European Patent  
Office

# EUROPEAN SEARCH REPORT

0005129

Application number

EP 79 85 0022

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int. Cl.)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
A	<u>DE - A - 2 548 340 (AB HRSSLE)</u>  * pages 1 to 12 *  -----	1, 24	C 07 D 403/12 A 61 K 31/44
			TECHNICAL FIELDS SEARCHED (Int. Cl.)
			C 07 D 403/12 A 61 K 31/44
			CATEGORY OF CITED DOCUMENTS
			X: particularly relevant A: technological background O: non-written disclosure P: intermediate document T: theory or principle underlying the invention E: conflicting application D: document cited in the application L: citation for other reasons
			&: member of the same patent family, corresponding document
<input checked="" type="checkbox"/> The present search report has been drawn up for all claims			
Place of search	Date of completion of the search	Examiner	
The Hague	18-07-1979	DE BUYSER	